IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

David R. LONG

Serial No.: 07/344,620 Group Art Unit: 125

Filed: April 28, 1989 Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

This is in response to the Official Action of June 28, 1989 in connection with the above-identified application. The period for response to the Official Action has been extended to expire on October 28, 1989 by the filing herewith of a Petition for a one-month extension of time and payment of the required fee.

Please amend the above-identified application as follows:

IN THE CLAIMS

Please amend claim 1 as follows:

1. (Amended) A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation ~~also containing~~ comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.

Please cancel claim 4 without prejudice or disclaimer.

REMARKS

Applicant has amended the claims as in the parent application in order to more particularly define the invention. The same 112 rejection was dropped in the parent application in view of these amendments.

More particularly, claims 1 and 4 have been combined and the amount of ethanol present has been functionally defined. Claim 4 has been cancelled from the application. The claims remaining in the application are Claims 1-3 and 5-10. Applicant most respectfully submits that all the claims how present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record.

The rejection of Claims 1-10 under 35 USC 112 second paragraph as being indefinite has been carefully considered. The expression "also containing ethanol" has been modified to specify that the amount of ethanol contained in the composition is a stabilizing amount of ethanol and this amendment is fully supported by applicant's specification, at page 2, lines 4 and 5.

In addition, the pH range from Claim 4 has been included in Claim 1. Applicant most respectfully submits that there is no requirement that the method of obtaining the pH be set forth in the claims. This would be fully appreciated by one of ordinary skill in the art. In fact, the desired pH can be simply achieved by adding an appropriate amount of a

physiologically acceptable acid or base to the solution, depending on whether the solution is prepared from ranitidine free base or an acid addition salt thereof. It is not necessary to use buffer salts to obtain the desired pH, although it may often be more convenient to do so. Accordingly, it can be seen that the means for adjusting pH are entirely conventional and therefore, it is most respectfully requested that this aspect of the rejection under 35 USC 112 be withdrawn. As far as Claim 7 is concerned, having inserted the pH range in Claim 1, the amount of buffer salts is thereby predetermined, depending on the specific buffer salts that are used.

The rejections of Claims 1-14 under 35 USC 103 as being unpatentable over Chemical Abstract has been carefully considered. In the Official Action it is urged that the art teaches the cojoining of ranitidine and an alcohol; e.g., ethanol. The addition of a non-critical pH limitation and non-critical amounts are not seen as patentable limitations to the various claims. This rejection having been carefully considered is most respectfully traversed.

At the outset, applicant specifically traverses the statement in the Official Action that the references relied upon by the Examiner teach the cojoining of ranitidine and an alcohol, e.g., ethanol. Applicant most respectfully submits that the art does not teach the cojoining of ranitidine and an alcohol in a pharmaceutical composition which is an aqueous formulation for oral administration. These references do not lead one of ordinary skill in the art any way to expect that

the stability of ranitidine in an aqueous oral formulation could be enhanced by the presence of ethanol and does not suggest the presence of ethanol in such compositions.

The first Chemical Abstract reference (97 61014G) relates to the Glaxo patent for a new polymorphic form of ranitidine hydrochloride (designated form 2) and includes a description of processes for its production. Applicant most respectfully submits that all that one of ordinary skill in the art can infer from this reference is that ranitidine hydrochloride must be reasonably stable in ethanol since ethanol is used as a solvent for recrystallization. However, there is no teaching whatever that the stability of ranitidine or its salts as an aqueous formulation for oral administration is enhanced by the presence of ethanol and no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed.

The second Chemical Abstract reference (104 102280z) relates to a paper in a Scandinavian journal indicating the presence of ethanol in a person's diet did not adversely effect the gastric acid secretion inhibiting properties of ranitidine. Again, there is absolutely no teaching in this reference that would lead one of ordinary skill in the art to expect that ethanol would enhance the stability of ranitidine in aqueous oral formulations or would suggest to one of ordinary skill in the art that ethanol should be added to such formulations.

In summary, the prior art relied upon in the rejection is in fact, extremely far removed from the present claimed

invention and no way renders it obvious. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicant wishes to reiterate that the stability of a pharmaceutical formulation for oral administration is the most important factor and enhancing the stability of the active ingredient of such formulations is always an objective. Thus, in the development of any pharmaceutical formulation, it is necessary to ensure that the drug substance is stable within the formulation and this is necessary for two main reasons. Firstly, the drug substance must be stable in order to ensure that the patient is receiving the correct dosage of the drug. Secondly, it is important to ensure that the patient is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This second point is particularly important since it is not always possible to identify fully all of the breakdown products that may occur. Consequently, the chronic toxicity of all of the various compounds arising from the breakdown of the drug substance cannot be determined.

In practice, degradation of the drug substance within a formulation usually occurs upon storage and is often dependent upon a number of factors including temperature and time of storage. Any improvement that can be made in enhancing the stability of the drug substance can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, enhancement of the stability of the drug substances also benefit from the economic point of view in that it increases the effective shelf life of the

product. There is not the remotest suggestion of this in the prior art of record.

Applicant would like to make of record an additional reference which has only recently come to the attention of applicant when the corresponding German specification was cited in connection with the corresponding application is Austria. This is UK Patent Application No. 2,120,938A. This specification relates to the combination of anti-ulcer drugs such as ranitidine together with salicylic acid or a salt thereof and optionally a non-steroidal anti-inflammatory. Page 7, lines 20-29 of this document refers to the formulations for parenteral administration and states that these may be formulated in water or organic solvents including a reference to lower aliphatic alcohols, optionally in admixture with water. However, there is absolutely no teaching which would lead one of ordinary skill in the art to select ethanol in combination with ranitidine in the expectation of providing an oral formulation which is stabilized by the presence of ethanol. Thus, this reference neither alone or in combination with any other reference anticipates or renders obvious the presently claimed invention.

In view of the above comments and amendments to the claims, favorable reconsideration and allowance of all of the

Claims now present in the application are most respectfully requested.

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500

Date: October 30, 1989

fact

Sheet 1 of 1

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
REF/Long/620	494,861 07/~~344,620~~

APPLICANT: David R. LONG

FILING DATE	GROUP
4/28/89	125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	2120938A	5/83	United Kingdom				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED
	11/11/97

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(12) UK Patent Application (19) GB (11) 2 120 938 A

(21) Application No 8313269
(22) Date of filing 13 May 1983
(30) Priority data
(31) 1535
1536
(32) 14 May 1982
14 May 1982
(33) Hungary (HU)
(43) Application published
14 Dec 1983
(51) INT CL³
A61K 31/19 31/33
(52) Domestic classification
A5B 170 180 190 296 29Y
327 380 381 38Y 392 401
40Y 420 421 42Y 441 444
446 44Y 451 452 453 45Y
480 481 482 483 485 48Y
501 503 50Y 511 51Y 523
52Y 540 541 542 54Y 550
551 552 55Y 565 566 56Y
575 576 57Y 586 58Y 606
60Y 616 61Y 650 653 65Y
660 664 66Y J
(56) Documents cited
None
(58) Field of search
A5B

(71) Applicants
Richter Gedeon
Vegyeszeti Gyar Rt,
(Hungary),
Gyomroi ut 19/21,
Budapest X,
Hungary.
(72) Inventors
Elemer Ezer,
Laszlo Szporny,
Judit Matuz,
Gyorgy Hajos,
Mariann Skvorecz,
Katalin Pallagi,
Eva Palosi,
Eszter Cholnoky,
Gyozo Hortobagyi.
(74) Agent and or Address for Service
Frank B. Dehn and Co.,
Imperial House,
15-19 Kingsway,
London WC2B 6UZ.

(54) **Anti-ulcer pharmaceutical compositions containing salicylic acid or its salts**

(57) The invention relates to new anti-ulcer and anti-ulcer/antiinflammatory compositions and products, which contain an anti-ulcer agent or a salt thereof and salicylic acid or an alkali metal salt thereof optionally together with a non-steroidal antiinflammatory agent. As an anti-ulcer agent preferably cimetidine or ranitidine is employed, while the preferred non-steroidal antiinflammatory agent is indomethacin.

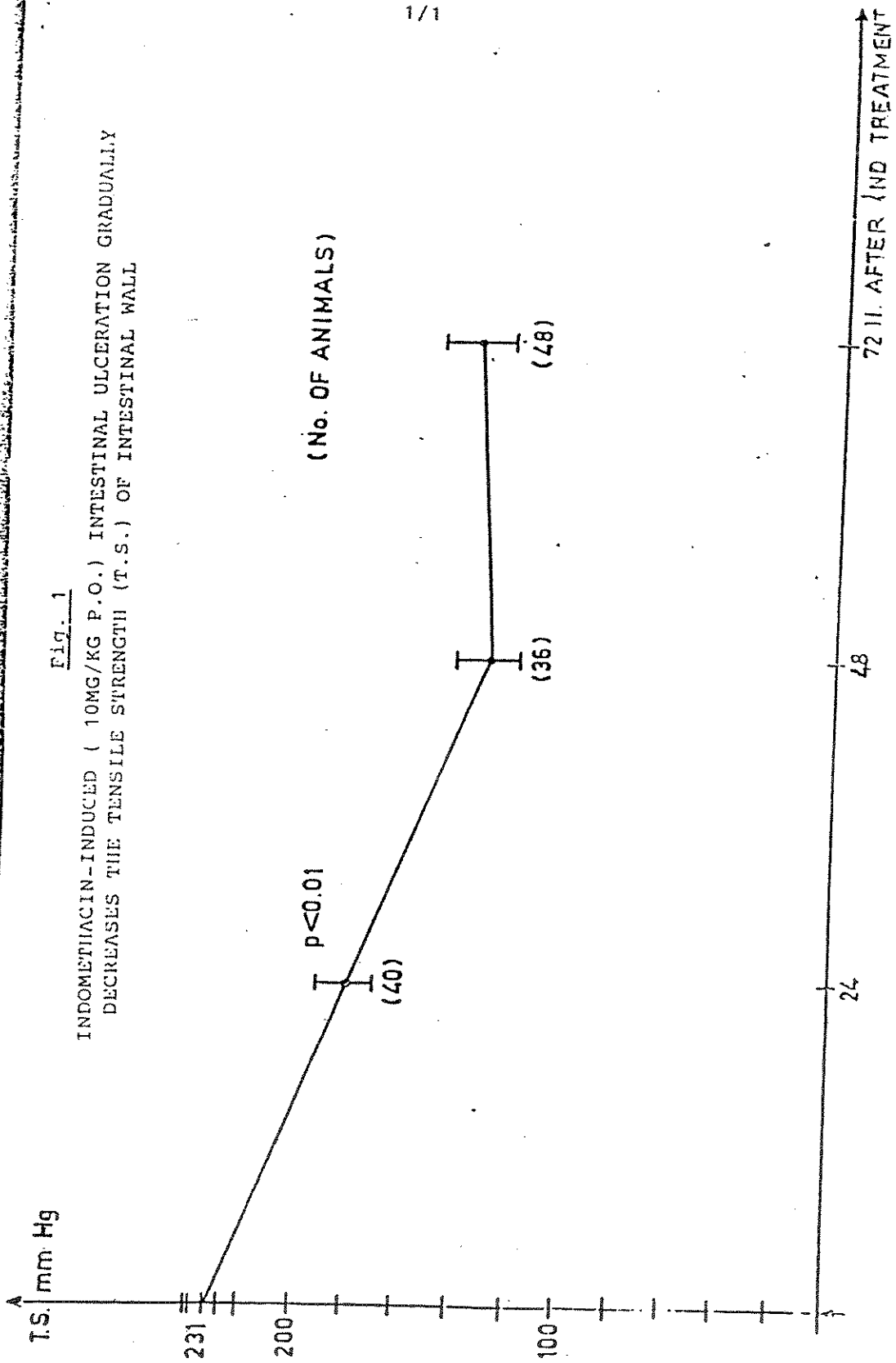
GB 2 120 938 A

2120938

1/1

Fig. 1

INDOMETHACIN-INDUCED (10MG/KG P.O.) INTESTINAL ULCERATION GRADUALLY DECREASES THE TENSILE STRENGTH (T.S.) OF INTESTINAL WALL



SPECIFICATION

Anti-ulcer pharmaceutical compositions

The invention relates to new anti-ulcer pharmaceutical compositions and a process for their preparation. More particularly, the invention concerns new pharmaceutical compositions containing two or more active ingredients which compositions are effective against gastrointestinal ulceration and, if desired, may also contain anti-inflammatory agents.

Since the H_2-receptor antagonists were first described, [Nature *236*, 385 (1962)] this novel group of anti-ulcer agents has been subjected to extensive experimental and clinical investigations. Shortly afterwards, cimetidine (N"-cyano-N'-methly-N-[2-(((5-methyl-1H-imidazolyl-4-yl)-methyl)-thio)-ethyl]-guanidine) appeared on the market and has been favourably received. In the past few years numerous new H_2-receptor antagonists have been prepared and investigated.

During the last few years, since the world-wide introduction of cimetidine, more than 1500 articles have been published concerning this agent. In experiments on rats it has been demonstrated for example by P. Del Soldato et al [Br. J. Pharmac. *67*, 33 (1979)] that cimetidine cannot prevent indomethacin-induced intestinal ulceration. Similar observations have recently been published by W.S. Mitchell et al [Brit. Med. J. *284*, 731 (1982)] following human clinical practice. It has been reported that the concurrent administration of cimetidine and indomethacin has resulted in perforated ulcers in the case of several patients.

It is well known that gastrointestinal ulcers, a typical disease peculiar to civilized communities, are occurring in more and more people. Among ulcerous patients there are numerous people suffering also from inflammatory or degenerative locomotor diseases. In such cases the medical attendant has to face a hitherto practically insoluble situation since until now no pharmaceutical composition was known in the art which could effectively be used under these conditions without serious side-effects. It is highly probable that the concurrent administration of an anti-ulcer agent and a non-steroidal antiinflammatory agent may accelerate the perforation of the ulcer.

It would thus be desirable to be able to provide a pharmaceutical composition which is devoid of these disadvantages and in which the activity of the anti-ulcer active ingredient is favourably increased, i.e. potentiated.

It is known that a common, undesired side-effect of non-steroidal antiinflammatory agents is their ulcerogenic effect. According to numerous publications 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-yl-acetic acid (indomethacin), 4-butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone), d-2-(6-methoxy-2-naphthyl)-propionic acid (naproxen), 3-(3-trifluoromethylanilino)-nicotinic acid (niflumic acid) and acetyl salicylic acid show an ulcerogenic side-effect. There are several methods by which the above undesired side-effect of antiinflammatory substances can be reduced. Our own experiments have showed that some reduction of side-effects can be achieved using certain salicylates (British Patent Specification 1,483,165) but there is no suggestion in the literature to combine these agents as anti-ulcer active ingredients; on the contrary, it is generally pointed out that the salicylates have an undesirable effect on the gastrointestinal condition (see for example: Aspirin and Related Drugs: Their Actions and Uses, K.D. Rainsford, K. Brune, M.W. Whitehouse, Birkhäuser Verlag, Basel und Stuttgart *1977*). Though different pharmacological investigations, recently carried out, have demonstrated unambiguously that sodium salicyate has a gastrointestinal cytoprotective effect (e.g. J. Pharm. Pharmac. *28*, 655 1976); Prostaglandins *21*, Suppl. 139 (1981)), it has also been reported that the gastrointestinal cytoprotective effect of sodium salicylate has no connection with gastric acid secretion (Adv. Physiol. Sci., Vol. 29, Gastrointestinal Defense Mechanisms, Pergamon Press - Akadémiai Kiadó, Budapest, Hungary, 1981).

We have found that in a concurrent administration of various antiinflammatory agents, particularly indomethacin, and cimetidine, the latter compound in a certain concentration range does not inhibit the intestinal ulcerogenic effect of the antiinflammatory agents, instead it facilitates this undesired action. Accordingly, it could not be expected that the administration of a certain dose of salicylic acid or a salicylate as a further component would almost entirely suppress the undesired side-effect.

The present invention is based on the surprising discovery that a combination of known anti-ulcer agents with sodium salicylate has a more significant, i.e. synergistic, anti-ulcer effect than the anti-ulcer agent alone. We have further found that when a non-steroidal antiinflammatory agent is added to such a combination, the undesired side-effects of the non-steroidal antiinflammatory agent can also be avoided.

According to one feature of the invention there are provided compositions comprising, as active ingredient, 1 part by weight of an anti-ulcer agent or a salt thereof and 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof. In one particular embodiment the active ingredient further includes 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent or a salt thereof. If desired, the compositions may also contain carriers and/or other additives such as are conveniently used in the pharmaceutical industry.

According to a preferred embodiment of the invention there are provided compositions wherein the anti-ulcer agent comprises cimetidine, ranitidine (N-[2-(((5-(dimethylamino)-methyl-2-furanyl)-methyl)-thio)-ethyl]-N'-methyl-2-nitro-1,1-ethylenediamine), propantheline (N,N-diisopropyl-N-methyl-2-(xanthene-9-carbonyloxy)-ethylammonium hydroxide), gastrixone (xanthene-9-carboxylic acid tropinester methyl hydrochloride) or zolimidine (2-(*p*-methylsulfonylphenyl)-imidazo[1,2-*a*]-pyridine).

According to a further preferred embodiment of the invention the pharmaceutical compositions contain, as a non-steroidal antiinflammatory agent, indomethacin, naproxen, phenylbutazone, acetylsalicilic acid or niflumic acid.

A preferred composition according to the invention may for example contain 0.1 to 1 part by weight of sodium salicylate, 1 part by weight of cimetidine and optionally 0.01 to 1 part by weight of indomethacin. Also preferred are compositions of 0.01 to 1 part by weight of sodium salicylate and 1 part by weight of cimetidine. The above compositions may additionally contain one or more conventional carriers and/or other additives.

In the compositions according to the invention the total active ingredient concentration preferably constitutes from 10 to 90% by weight of the total weight of the composition, the remainder consisting of carriers and/or other additives.

The invention further relates to a process for the preparation of these pharmaceutical compositions, which comprises mixing 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof with 1 part by weight of an anti-ulcer agent or a salt thereof, optionally together with 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent and/or with carriers and/or with other additives.

According to a preferred embodiment of the process 1 part by weight of cimetidine is mixed with 0.1 to 1 part by weight of sodium salicylate optionally together with one or more conventional carriers and/or additives; or 0.1 to 1 part by weight of sodium salicylate and 0.1 to 1 part by weight of indomethacin are mixed with 1 part by weight of cimetidine optionally together with one or more conventional carriers and/or other additives; or 1 part by weight of ranitidine is mixed with 0.1 to 10 parts by weight of sodium salicylate optionally together with one or more conventional carriers and/or other additives.

According to a further aspect of the present invention there is provided a pharmaceutical product comprising a first container containing salicyclic acid or an alkali metal salt thereof and a second container containing an anti-ulcer agent or a salt thereof in association with written or printed directions to administer the contents of the first and second containers concurrently in an amount of 0.1 to 10 parts by weight of salicyclic acid or salt thereof to 1 part by weight of anti-ulcer agent or salt thereof. If desired the product may further include a non-steroidal antiinflammatory agent such as described hereinabove in which case the directions will further indicate that the non-steroidal antiinflammatory agent be administered concurrently with the contents of the first and second containers in an amount of 0.01 to 1 part by weight of non-steroidal antiinflammatory agent to 1 part by weight of anti-ulcer agent or salt thereof. The anti-ulcer agent or salt thereof and the salicylic acid or alkali metal salt thereof, together with, if present, the antiinflammatory agent and/or any carriers and/or other additives, may either be admixed prior to administration or alternatively they may be administered to the patient immediately concurrently e.g. as tablets taken one after the other.

EXPERIMENTAL METHODS

1) *Indomethacin-induced intestinal ulceration*

Non-fasted Hannover-Wistar rats, each weighing 120-150 g., were given a 15 mg./kg. dose of indomethacin in a Tween 80 suspension to induce fatal intestinal ulceration. The test material was administered immediately after the indomethacin treatment, also orally.

To evaluate the development of small intestinal ulcers, the tensile strength of the intestinal wall was determined by the so-called inflation technique [J. Pharm. Pharmac. *27*, 867 (1975)], because the erosion caused by ulcerogenesis leads to a weakening of the strength of the intestinal wall. The animals were killed 48 and 72 hours, respectively, after the indomethacin treatment by ether narcosis. The small intestine from pylorus to caecum was carefully removed and one end was ligated, while the other end was connected to a W+W electronic BP Recorder 8005 (Ugo Basile, Italy) through a polyethylene tube. The entire small intestine was placed into a physiological saline solution at 37°C and the pressure increased until air bubbles appeared at the weakened sites in the intestinal wall. This pressure, expressed in mmHg, is defined as the tensile strength (T.S.). Parallel with the progress of the indomethacin-induced intestinal ulceration the tensile strength of the intestinal wall, also called intestinal wall resistancy, gradually decreases as illustrated in Figure 1 of the accompanying drawings.

2) *Abs. alcohol-induced gastric necrosis*

Gastric necrosis was induced by acidic-alcohol, by the modified method of Robert et al. [Gastroenterology 77, 433 (1979)]. Female Hannover-Wistar rats, each weighing 120-150 g., were fasted for 24 hours. Water was allowed *ad libitum*.

Compounds to be tested were administered orally 30 minutes prior to acidic-alcohol administration. Acidic-alcohol (cc. HCl:abs.ethanol = 1:50 v/v) was administered orally through a canula in a dose of 0.5 ml. pro 100 g. of body weight. Two hours later the animals were killed by ether overdose. Stomachs were removed and opened along the major curvature. The lesions induced by ethanol are located at the corpus of the stomach as multiple linear hemorrhagic bands of necrotic tissue. Lengths of the lesions were measured and expressed in mm.-s and the total length of lesions of each stomach was calculated. Degree of lesion severity was expressed as the mean of total lesion-length per stomach. The stomach cytoprotection was expressed in comparison with the control animals.

3) *Gastric acid secretion in Shay-rats*

The tests were carried out according to the method of Shay et al. [Gastroenterology 5, 43-46 (1945)]. Female Wistar rats, each weighing 120-150 g., were used. Pyrolic ligation was performed under ether anaesthesia after twenty-four hours' fasting. The animals were treated by the compounds to be tested intraperitoneally, immediately after the surgical intervention. The oral treatments were performed 30 minutes prior to operation. The animals were killed 4 hours after pyrolic ligation. After extension of the stomach the volume of gastric juice was measured and HCl concentration was determined by titration against 0.01 N NaOh in the presence of phenolphtalein as indicator. The amount of acid was expressed in µmoles per 100 g. of body weight. The statistical evaluation of the results was performed by Student's test.

Evaluation of the experimental results

By the above experiments the optimal cimetidine/sodium salicylate ratio, by which the indomethacin-induced intestinal ulceration (10 mg./kg.) and the gastric-acid secretion on Shay-rats could be inhibited was determined.

TABLE 1

Inhibition of Indomethacin-induced intestinal ulceration after concurrent administration of combinations of Cimetidine-Sodium-Salicylate in different ratios

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 48 hours after treat. in mmHg*	*Resistance of intestinal wall in percent of untreated value*
Untreated	30	-	231 ± 4	100
Indomethacin(Ind.)	26	10	111 ± 10	48^{xx}
Cimetidine (Cim.)	9	100	227 ± 1	98
Ind. + Cim.	10	10+100	63 ± 11	27^{xx}
Ind.+Cim.+Na−Salicylate	10	10+/100+10/	157 ± 28	68^{x}
Ind.+Cim.+Na−Salicylate	10	10+/100+25/	158 ± 19	68^{x}
Ind.+Cim.+Na−Salicylate	10	10+/100+50/	213 ± 7	94^{x}

x_p < 0.01 compared with Ind.+Cim. group
xx_p < 0.01 compared with untreated group

TABLE 2

Inhibition of gastric acid secretion by cimetidine and various combinations of cimetidine with Na-Salicylate on Shay-rats

Treatment	*n*	*Dose mg./kg.*	*HCl/4 hours µmoles/100 g. bwt. ± S.E.M.*	*Inhibition of HCl-production in percent*
Control	10	-	457 ± 55	-
Cimetidine (Cimet.)	10	50	163 ± 41	65^{x}
Cimet. + Na-Salicylate	10	50 + 10	172 ± 32	63^{x}
Cimet. + Na-Salicylate	10	50 + 25	40 ± 28	93^{xx}
Cimet. + Na-Salicylate	10	50 + 50	150 ± 42	68^{x}

x_p < 0.01 compared with the control
xx_p < 0.01 compared with the cimetidine 50 mg./kg. group

TABLE 3

In an abs.alcohol-induced gastric necrosis test Na-Salicylate is cytoprotective even in combination with cimetidine

Treatment	*n*	*Dose mg./kg. p.o.*	*Cytoprotection in % of the combination*	*Remarks*
Na-Salicylate	10	4	35	ED_{50} = 7.9
Na-Salicylate	10	8	60x	EE_{50} by A. Robert 15 mg./kg. Prostaglandins Suppl. 21. 1981. p. 139-146
Na-Salicylate	10	16	58x	
Na-Salicylate	10	16	94x	
Cimetidine (Cim.)				
Cim. + Na-Salicylate	10	8 + 4	5	
Cim. + Na-Salicylate	10	16 + 8	41x	ED_{50} = 30 this contains: 10 mg. of sodium-salicylate
Cim. + Na-Salicylate	10	32 + 16	82x	
Cim. + Na-Salicylate	10	64 + 32	93x	

According to the literature cimetidine is not protective in this test (Hagel et al.: Gastroenterology, 82.No.5. Suppl. 2. 1078, 1982; Soldato P.Del: Boll. Chim. Farm. 120, No.11, 631-638. 1981)

x $p < 0.01$

TABLE 4

Intestinal ulceration after repeated treatment (on three consecutive days) with Indomethacin, Cimetidine and combination of Cimetidine and Na-Salicylate (2:1)

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 24 hours after last treat. in mmHg*	*Mortality in percent*	*Resistance of intestinal wall in per-cent of un-treated value*
Untreated (normal)	30	-	231 ± 4	-	100
Indomethacin (Ind.)	10	3 × 10	20 ± 10	30	9
Cimetidine (Cim.)	10	3 × 100	186 ± 16	0	80
Ind. + Cim.	10	3 × (10+100)	9 ± 15	50	4
Ind. + Cim. + Na-Salicylate 2:1	10	3 × (10+100+50)	225 ± 6	0	97x

x $p < 0.01$ compared with Ind. group

TABLE 5

Inhibition of gastric acid secretion in pylorus-ligated rats by Cimetidine and combination of Cimetidine and Na-Salicylate (2:1) treatment

Treatment	*n*	*Dose mg./kg. i.p.*	*HCl output 4 hours µmol/100 g. bwt.*	*Inhibition of HCl output %*	*Remark*
Control	40	-	425 ± 23	-	
Sodium-Salicylate	5	25	420 ± 47	0	
Sodium-Salicylate	5	50	381 ± 75	11	
Cimetidine	10	15	378 ± 55	12	
Cimetidine	10	25	327 ± 50	33	
Cimetidine	10	50	259 ± 62	39	ED_{50}=54.4
Cimetidine	5	100	140 ± 38	67	

TABLE 6

Inhibition of gastric acid secretion in Shay-rats by treatment with a 2:1 combination of Cimetidine and Na-Salicylate

Treatment	*n*	*Dose mg./kg. i.p.*	*HCl output/4 hours µmol/100 g. bwt ± S.E.M.*	*HCl output inhibition in %*	*Remark*
Control	9	-	435 ± 36	-	
Cim. + Na-Salicylate	10	6 + 3	316 ± 45	28	
Cim. + Na-Salicylate	10	12 + 6	374 ± 40	14	
Cim. + Na-Salicylate	10	24 + 12	256 ± 36	48x	
Cim. + Na-Salicylate	20	50 + 25	156 ± 18	64x	ED_{50} = 35.6, which contains: Cim. = 23.8 mg. Na-Salicylate = = 11.8 mg.
Cim. + Na-Salicylate	5	64 + 32	0	100	

$x_p < 0.01$ compared with the control

TABLE 7

Inhibition of Indomethacin-induced fatal intestinal ulceration after concurrent administration of various anti-ulcer compounds

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 72 hours after treat. in mmHg*	*Resistance of intestinal wall in % of untreated value*	*Mortality in percent*
Untreated	30	-	231 ± 4	100	-
Indomethacin (Ind.)	26	15	66 ± 13	28x	20
Ind. + Propantheline	10	15+20	48 ± 10	21x	20
Ind. + Gastrixon	10	15+20	57 ± 15	25x	10
Ind. + Zolimidine	10	15+100	45 ± 15	19x	-
Ind. + Cimetidine	9	15+150	47 ± 10	20x	10
Ind. + Ranitidine	10	15+50	100 ± 20	43x	-

$x_p < 0.01$ compared with untreated group

TABLE 8

Inhibition of Indomethacin-induced ulceration after concurrent administration of Ranitidine and Sodium-Salicylate

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 48 hours after treat. in mmHg*
Untreated	30	-	231 ± 5
Ranitidine (Ran.)	9	25	225 ± 8
Indomethacin (Ind.)	26	10	111 ± 10
Ind. + Ran.	9	10 + 25	145 ± 18
Ind. + Ran. + Na-Salicylate	10	10 + 25 + 100	219 ± 5x

$x_p < 0.01$ compared with Ind. group

TABLE 9

Inhibition of intestinal ulceration induced by a 15 mg.kg. p.o. dose of indomethacin by concurrent administration of sodium-salicylate and various anti-ulcer agents

Treatment	*n*	*Dose mg./kg p.o.*	*Tensile strength of s.intestine, 72 hours after treat., in mmHg*	*Resistance of intestinal wall in % of untreated value*	*Mortality in percent*
untreated (normal)	30	-	231 ± 5	100	-
Indomethacin (Ind.)	26	15	66 ± 10^{x}	28^{x}	20
Ind.+Propantheline (Prop.)	10	15+20	48 ± 10^{x}	21^{x}	20
Ind.+(Prop.+Na-Salic.)	10	15+(20+100)	211 ± 6^{xx}	91^{xx}	-
Ind.+Gastrixon (Gas.)	10	15+20	57 ± 15^{x}	25^{x}	10
Ind.+(Gas.+Na-Salic.)	10	15+(20+100)	211 ± 4^{xx}	96^{xx}	-
Ind.+Zolimidine (Zol.)	10	15+100	45 ± 13^{x}	19^{x}	-
Ind.+(Zol.+Na-Salic.)	10	15+(100+100)	207 ± 11^{xx}	89^{xx}	-

x_p 0.01 compared with the untreated group
xx_p 0.01 compared with indomethacin

The data set forth in Tables 1 - 2 show that the optimal ratio between cimetidine and sodium salicylate was 2:1.

In Figure 1 the time course of the intestinal ulceration induced by a 10 mg./kg. dose of indomethacin is illustrated.

Table 3 shows that a 2:1 combination of cimetidine and Na-Salicylate has a dose-dependent cytoprotective effect against abs.alcohol-induced stomach necrosis while cimetidine is not cytoprotective.

As set forth in Table 4 the intestinal toxicity of indomethacin was markedly apparent after repeated treatment on three consecutive days (3×10 mg./kg. p.o.) and the mortality was found to be 30 percent on the fourth day. Concurrent administration of 3×100 mg./kg. cimetidine p.o. resulted in a greater intestinal toxicity (mortality 50 %). Concurrent administration of 3×(100÷50) mg./kg. of cimetidine and Na-Salicylate (2:1) p.o. results in an absolute blockade of intestinal toxicity.

One of the most important factors, the gastric acid secretion has been investigated in detail by using Shay-rats. The results are summarized in Tables 5 and 6. Both cimetidine and the combination of cimetidine and Na-Salicylate (2:1) have dose dependent inhibitory effect on the gastric acid secretion. The ED_{50} values for cimetidine and the combination of cimetidine and Na-Salicylate (2:1) were 54.4 mg./kg. i.p. and 35.6 mg./kg. i.p., respectively. The 35.6 mg. of the combination of cimetidine and Na-Salicylate (2:1) contained 23.8 mg. of cimetidine and 11.8 mg. of sodium salicylate. In combination a dose of cimetidine 56% less than that of cimetidine alone produced the same (50%) gastric acid secretion. Sodium salicylate alone was actually ineffective as a gastric acid inhibitor. The results were similar in case of intraperitoneal and oral treatment, respectively. The results show that a *synergism* exists between cimetidine and salicylate, as to the inhibition of gastric acid secretion.

From Table 7 it appears that the concurrent administration of the tested anti-ulcer compounds cannot block the indomethacin-induced fatal intestinal ulceration.

According to the data in Table 8 a combination of ranitidine with sodium salicylate (25÷100 mg./kg.) results in a total inhibition of intestinal ulceration induced by a 15 mg./kg. p.o. dose of indomethacin.

The results obtained with combinations of various further anti-ulcer compounds and of sodium salicylate are shown in Table 9. It can be seen that while the anti-ulcer compounds listed in Table 7 alone are ineffective, in a combination with the cytoprotective sodium salicylate they can effectively block the intestinal ulceration induced with indomethacin.

According to a preferred embodiment of the invention a combination of 200 mg. cimetidine and 100 mg. sodium salicylate is used in one tablet. Instead of sodium salicylate salicylic acid or lithium salicylate can equally be used.

The pharmaceutical compositions according to the invention can be administered orally, rectally and/or parenterally, in a single daily dose or in several smaller doses. For oral administration the compositions are generally formulated as tablets, preferably coated tablets, dragées or capsules. The oral formulations according to the invention generally do not contain any excipient but, if desired, excipients like lactose or starch can also be employed. As a binding material for example gelatine, sodium carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone or starch gum can be used. As a disintegrating agent preferably potato starch or microcrystalline cellulose are added into the compositions but ultraamylopectin or formaldehyde caseine, etc. can also be employed. As a lubricant and anti-adhesive talc, colloidal silicic acid, stearine, calcium or magnesium stearate, etc. can be used.

Such tablets may be prepared by the conventional techniques of the pharmaceutical industry, e.g. by

granulation and subsequent pressing. Thus the mixture of active ingredients and fillers and optionally a part of the disintegrating substances may be granulated with an aqueous, alcoholic or aqueous-alcoholic solution of the binding agents in a suitable apparatus and the granules obtained dried. The dry granulate may then be mixed with the further additives, e.g. disintegrating, anti-adhesive agents and lubricants, and the mixture pressed into tablets. If desired, to facilitate administration the tablets are grooved. The tablets can be coated with a gastric acid resistant film, e.g. shellac, cellulose acetate phthalate or Eudragit-L using an alcoholic, preferably isopropanolic solution of the film-forming materials. The tablets can be prepared from a mixture of the active ingredients and additives directly by pressing, and the tablets obtained can be coated with an intestino-solvent film layer.

Degées can be prepared by using various protecting, flavouring agents and pigments conventionally used in the preparation of pharmaceuticals, e.g. sugar, cellulose derivatives (methyl or ethyl cellulose, carboxymethyl cellulose sodium, etc.), polyvinylpyrrolidone, calcium phosphate, calcium carbonate, food-pigments, food-colour shellacs, iron oxide pigments, aroma substances, etc.

Capsules can for example be prepared by filling a mixture of the active ingredients and additives into a hard gelatine capsule.

For rectal administration suppositories may be prepared. As a carrier vegetable fats, e.g. hardened vegetable oils or triglycerides of fatty acids having 12 to 17 carbon atoms, preferably Witepsol are employed. The active ingredients are preferably homogeneouslydistributed in the melted mass of the carriers and suppositories are prepared therefrom by moulding.

For parenteral administration injectable preparations are prepared. The active ingredients may be dissolved in water or organic solvents, optionally in the presence of mediators, e.g. polyoxyethylene sorbitan monolaurate, monooleate or monostearate (Tween-20, Tween-60 and Tween-80, respectively,). As an organic solvent for example lower aliphatic alcohols or glycol ethers, preferably ethyleneglycol monoethyl ether, can be employed, optionally in admixture with water. The injectable solutions may contain also various auxiliary agents, such as preservatives, e.g. benzyl alcohol, *p*-hydroxybenzoic acid methyl and/or propyl ester, phenylmercuriborate or benzalconium chloride, or antioxidants, such as sodium pyrosulfate, ascorbic acid, tocopherol and optionally complexing agents to bind trace metals, e.g. ethylenediamine tetraacetic acid, and pH-adjusting and buffer materials, and optionally local anaesthetics, e.g. lidocaine.

The injectable solutions according to the invention are preferably filtered prior to filling into ampoules and are then subjected to sterilization.

The invention will further be illustrated by the following specific Examples which are for illustration only and not limitation of our invention.

Example 1

Cimetidine-sodium salicylate tablets

cimetidine	200 mg.
sodium salicylate	100 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

From the materials listed above 350 mg. tablets are prepared by wet granulation and moulding. Essentially the same activity is obtained if in the above composition sodium salicylate is replaced by an equivalent amount of another alkali metal salicylate, e.g. lithium salicylate.

Examples 2 to 16

In the following Examples 2-16, tablets are prepared as in Example 1 except the active components and ingredients are present in the amounts specified below. The manufacturing procedure is the same as in Example 1. is the same as in Example 1.

Example 2

ranitidine	50 mg.
sodium salicylate	100 mg.
potato starch	8 mg.
magnesium stearate	1 mg.
polyvinylpyrrolidone	3 mg.
talc	3 mg.

Example 3

propantheline	15 mg.
sodium salicylate	75 mg.
magnesium stearate	2 mg.
potato starch	8 mg.
polyvinylpyrrolidone	2.5 mg.
talc	2.5 mg.

Example 4

gastrixone	2 mg.
sodium salicylate	25 mg.
magnesium stearate	1 mg.
potato starch	1 mg.
polyvinylpyrrolidone	0.5 mg.
talc	0.5 mg.

Example 5

zolimidine	200 mg.
sodium salicylate	100 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

Example 6

cimetidine	200 mg.
sodium salicylate	100 mg.
indomethacin	20 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

Example 7

cimetidine	200 mg.
sodium salicylate	100 mg.
naproxen	200 mg.
magnesium stearate	5 mg.
polyvinylpyrrolidone	3 mg.
potato starch	37 mg.
talc	15 mg.

Example 8

cimetidine	200 mg.
sodium salicylate	100 mg.
phenylbutazone	100 mg.
potato starch	40 mg.
talc	12 mg.
polyvinylpyrrolidone	12 mg.
magnesium stearate	4 mg.

Example 9

cimetidine	200 mg.
sodium salicylate	100 mg.
aspirin	200 mg.
potato starch	40 mg.
talc	20 mg.
polyvinylpyrrolidone	15 mg.
magnesium stearate	5 mg.

Example 10

cimetidine	200 mg.
sodium salicylate	100 mg.
niflumic acid	200 mg.
potato starch	40 mg.
talc	20 mg.
polyvinylpyrrolidone	15 mg.
magnesium stearate	5 mg.

Example 11

ranitidine	50 mg.
sodium salicylate	100 mg.
indomethacin	20 mg.
potato starch	15 mg.
polyvinylpyrrolidone	6 mg.
talc	6 mg.
magnesium stearate	3 mg.

Example 12

ranitidine	50 mg.
sodium salicylate	100 mg.
naproxen	150 mg.
potato starch	25 mg.
talc	10 mg.
polyvinylpyrrolidone	10 mg.
magnesium stearate	5 mg.

Example 13

ranitidine	50 mg.
sodium salicylate	100 mg.
phenylbutazone	100 mg.
potato starch	14 mg.
talc	6 mg.
polyvinylpyrrolidone	8 mg.
magnesium	2 mg.

Example 14

ranitidine	50 mg.
sodium salicylate	100 mg.
aspirin	200 mg.
potato starch	30 mg.
talc	10 mg.
polyvinylpyrrolidone	8 mg.
magnesium stearate	2 mg.

Example 15

ranitidine	50 mg.
sodium salicylate	100 mg.
niflumic acid	200 mg.
potato starch	30 mg.
talc	10 mg.
polyvinylpyrrolidone	8 mg.
magnesium stearate	2 mg.

Example 16

propantheline	15 mg.
sodium salicylate	150 mg.
indomethacin	20 mg.
potato starch	15 mg.
talc	5 mg.
polyvinylpryrrolidone	4 mg.
magnesium stearate	1 mg.

CLAIMS

1. Pharmaceutical compositions comprising, as active ingredient, 1 part by weight of an anti-ulcer agent or a salt thereof and 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof.
2. Compositions as claimed in claim 1 further including, as an active ingredient, 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent.
3. A composition as claimed in claim 2 wherein the non-steroidal antiinflammatory agent comprises indomethacin, naproxen, phenylbutazone, acetyl-salicylic acid or niflumic acid.
4. Compositions as claimed in any preceding claim wherein the anti-ulcer agent comprises cimetidine, ranitidine, propantheline, gastrixone or zolimidine.
5. Pharmaceutical compositions comprising 0.1 to 1 part by weight of sodium salicylate and 1 part by weight of cimetidine in combination with one or more carriers and/or other additives.
6. Pharmaceutical compositions comprising 0.1 to 1 parts by weight of sodium salicyate, 0.01 to 1 part by weight of indomethacin and 1 part by weight of cimetidine, in combination with one or more carriers and/or other additives.
7. Pharmaceutical compositions comprising 0.1 to 10 parts by weight of sodium salicylate and 1 part by weight of rantidine, in combination with one or more carriers and/or other additives.
8. Compositions as claimed in any preceding claim in which the total active ingredient concentration constitutes from 10 to 90% by weight of the total weight of the composition, the remainder consisting of one or more carriers and/or other additives.
9. Pharmaceutical compositions as claimed in claim 1 or claim 2 substantially as herein described.
10. Pharmaceutical compositions substantially as herein described in any one of Examples 1 to 16.
11. A process for the preparation of a pharmaceutical composition which comprises mixing 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof with 1 part by weight of an anti-ulcer agent or a salt thereof optionally together with 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent and/or with one or more carriers and/or other additives.
12. A process as claimed in claim 11 wherein the anti-ulcer agent is cimetidine, ranitidine, propantheline, gastrixone or zolimidine and the optional non-steroidal antiinflammatory agent is indomethacin, naproxen, phenylbutazone, acetyl-salicylic acid or niflumic acid or a salt thereof.
13. A process as claimed in claim 12 wherein 0.1 to 1 part by weight of sodium salicylate is mixed with 1 part by weight of cimetidine.
14. A process as claimed in claim 12 wherein 0.1 to 1 part by weight of sodium salicylate is mixed with 0.01 to 1 part by weight of indomethacin and 1 part by weight of cimetidine.
15. A process as claimed in claim 12 wherein 0.1 to 10 parts by weight of sodium salicylate are mixed with 1 part by weight of ranitidine.
16. A process as claimed in claim 11 substantially as herein described.
17. A process as claimed in claim 11 substantially as herein described in any one of Examples 1 to 16.
18. Pharamaceutical compositions whenever prepared by a process as claimed in any one of claims 11 to 17.
19. A pharmaceutical product comprising a first container containing salicylic acid or an alkali metal salt thereof and a second container containing an anti-ulcer agent or a salt thereof in association with written or printed directions to administer the contents of the first and second containers concurrently in an amount of 0.01 to 10 parts by weight of salicylic acid or salt thereof to 1 part by weight of anti-ulcer agent or salt thereof.

20. A product as claimed in claim 19 further including a non-steroidal antiinflammatory agent and wherein the directions indicate that the non-steroidal antiinflammatory agent be administered concurrently with the contents of the first and second containers in an amount of 0.01 to 1 part by weight of non-steroidal antiinflammatory agent to 1 part by weight of anti-ulcer agent or salt thereof.

21. Each and every novel method, process, composition and product herein disclosed.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1983.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/344,620 04/28/89 LUKE C REF/PAUL

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE, FOURTH FLOOR
ALEXANDRIA, VA 22314

FRIEDMAN, S

425 6

11/14/89

☒ This application has been examined ☒ Responsive to communication filed on 10/30/89 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3 + 5-14 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims all are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

44

EXAMINER'S ACTION

PTOL-326 (Rev. 6-88)

Claims 1-3 and 5-10 remain rejected under the 2nd paragraph for the reasons of record. The presence of "also" (claim 1) leaves open the question what other ingredients might be intended.

Claims 1-3 and 5-10 remain rejected under 35 USC 112, 1st paragraph for the reasons of record. The claims are silent as to the amount of ranitidine present. It is 10 grams, 5 mg., an effective amount or what? We don't know. Page 3 states an amount. The claims are broader than this.

All claims remain rejected under 35 USC 103 for the reasons clearly of record. Chem. Abst. 104 clearly shows ranitidine administered in the presence of ETOH and obviously the mixture is aqueous. Chem. Abst. 97- shows ranitidine with an alcohol (2-propanol). This art clearly precludes applicants claims to ranitidine and ETOH. (A) 104- teaches the ingredients together in the presence of each other. (B) 97- does show an alcohol and ranitidine in a formulation. As for the allegation of enhanced stability, it has not been demonstrated for the compositions urged as contrasted with any of other pH parameters.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE (3) MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO (2) MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE (3) MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX (6) MONTHS FROM THE DATE OF THIS FINAL ACTION.

FRIEDMAN:cwh

A/C 703

557-3920

11-13-89

...ley J. Friedman
Primary Examiner
Art Unit 1...

#620 115

6p175 #1 3/27/90

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 07/344,620

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: April 28, 1989

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

RECEIVED
90 MAR 26 PM 2:41
GROUP 120

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

[x] one month [ ] three months
[ ] two months [ ] four months

The fee set in 37 CFR 1.17 for the extension of time is $ 62 .

[x] Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200 . A duplicate copy of this paper is enclosed.

[ ] Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

[ ] Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

[ ] has been filed [ ] is enclosed

Also enclosed is a:

[ ] Response [ ] Notice of Appeal [ ] Appeal Brief

[x] Rule 1.62 File Wrapper Continuation Application w/$370

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500

March 14, 1990

140 03/16/90 07344620 1 115 62.00 CK

3700

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

101
07/494904
A
S/C
JH1
4/26/4

REQUEST FOR FILING FILE WRAPPER CONTINUATION APPLICATION UNDER 37 C.F.R. 1.62

Honorable Commissioner of
Patents and Trademarks
Box FWC
Washington, D.C. 20231

Sir:

This is a request for filing a FILE WRAPPER CONTINUATION under 37 C.F.R. 1.62 of pending prior application:

SERIAL NO.: 07/344,620 GROUP ART UNIT: 125

FILED: April 28, 1989 EXAMINER: Friedman

INVENTOR: LONG

TITLE: PHARMACEUTICAL COMPOSITIONS

by the following inventors:

Full Name of Inventor: David Richard Long
Residence: 41, Echo Hill
City: Royston, Hertfordshire
State or Country: ENGLAND

Full Name of Inventor:
Residence:
City:
State or Country:

Full Name of Inventor:
Residence:
City:
State or Country:

Full Name of Inventor:

Residence:

City:

State or Country:

The above-identified prior application in which no payment of the issue fee, abandonment of, or termination of proceedings has occurred, is hereby expressly abandoned as of the filing date of this new application. Please use all the contents of the prior application file wrapper, including the drawings, as the basic papers for the new application.

_____ A preliminary amendment is enclosed.

__X__ The filing fee is calculated as shown below:

ITEM AS FILED*		NO. EXTRA		SMALL ENTITY		FULL FEE
Basic Fee				$185		$370
Total Claims	13-20=	0	x$ 6=		x$12=	0
Indep Claims	2- 3=	0	x$18=		x$36=	0
	TOTAL			$		$ 370

*Note: All calculations are based on condition of claims after any Preliminary Amendment made pursuant to this communication

__X__ A check in the amount of $ 370 is enclosed.

__X__ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. 1.16, except claim fees under 1.16(b), (c) or (d) associated with this communication, or credit any overpayment to Deposit Account No. 02-0200. A duplicate copy of this sheet is enclosed.

_____ Applicant is a small entity and is entitled to pay reduced fees in this application. A verified small entity statement was filed in _____ on _____.

__X__ Amend the specification by inserting before the first line the sentence: This application is a CONTINUATION of application Serial No. 07/344,620, filed April 28, 1989, now abandoned, which is a continuation of serial no. 07/131,442, filed December 11, 1987, now abandoned.

__X__ Priority is claimed under 35 U.S.C. § 119 of application(s):

Serial No. 86 29781, filed 12 Dec. 1986 in United Kingdom
Serial No. _____, filed _____ in _____

X The certified copy has been filed in prior application Serial No. 07/131,442 filed Dec. 11, 1987.

X The prior application is assigned of record to GLAXO GROUP LIMITED

X Also enclosed Petition for one month extension of time w/$62

X The power of attorney appears in the original papers in the prior application, and the power of attorney in the prior application includes:
Richard E. Fichter, Reg. No. 26,382 of Bacon & Thomas

It is understood that secrecy under 35 U.S.C. 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 C.F.R. 1.62 application, be it either this application or a prior application in the same file wrapper, the Patent and Trademark Office may provide similar information or access to all the other applications in the same file wrapper.

X Address all future communications to:

Richard E. Fichter
BACON & THOMAS
625 Slaters Lane, Fourth Floor
Alexandria, Virginia 22314

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382
Attorney of Record

BACON & THOMAS
625 Slaters Lane
Fourth Floor
Alexandria, VA 22314
(703) 683-0500

Date: March 14, 1990

FORM PTO-875 — U.S. DEPARTMENT OF COMMERCE — PATENT AND TRADEMARK OFFICE

PATENT APPLICATION FEE DETERMINATION RECORD

SERIAL NO	FILING DATE
494504	03/14/90
APPLICANT (FIRST NAMED)	
Long, David R	

CLAIMS AS FILED - PART I

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY FEE
BASIC FEE				185	OR		370
TOTAL CLAIMS	13 - 20*	*	x 6		OR	x 12	
INDEP. CLAIMS	2 - 3*	*	x18		OR	x 36	
MULTIPLE DEPENDENT CLAIM PRESENT			60		OR	120	
			TOTAL		OR	TOTAL	370

* If the difference is zero or less, enter "0" on line 2

CLAIMS AS AMENDED - PART II

	(1) CLAIMS REMAINING AFTER AMENDMENT	(2) HIGHEST NO. PREVIOUSLY PAID FOR	(3) PRESENT EXTRA
AMENDMENT A — TOTAL	12	20	—
AMENDMENT A — INDEP.	2	3	—
AMENDMENT A — FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			
AMENDMENT B — TOTAL			
AMENDMENT B — INDEP.			
AMENDMENT B — FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			
AMENDMENT C — TOTAL			
AMENDMENT C — INDEP.			
AMENDMENT C — FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			

	SMALL ENTITY RATE	SMALL ENTITY ADDIT. FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDIT. FEE
AMENDMENT A	x 6		OR	x 12	—
	x 18			x 36	—
	60			120	
	TOTAL ADDIT. FEE		OR	TOTAL	—
AMENDMENT B	x 6		OR	x 12	
	x 18			x 36	
	60			120	
	TOTAL ADDIT. FEE		OR	TOTAL	
AMENDMENT C	x 6		OR	x 12	
	x 18			x 18	
	60			60	
	TOTAL ADDIT. FEE		OR	TOTAL	

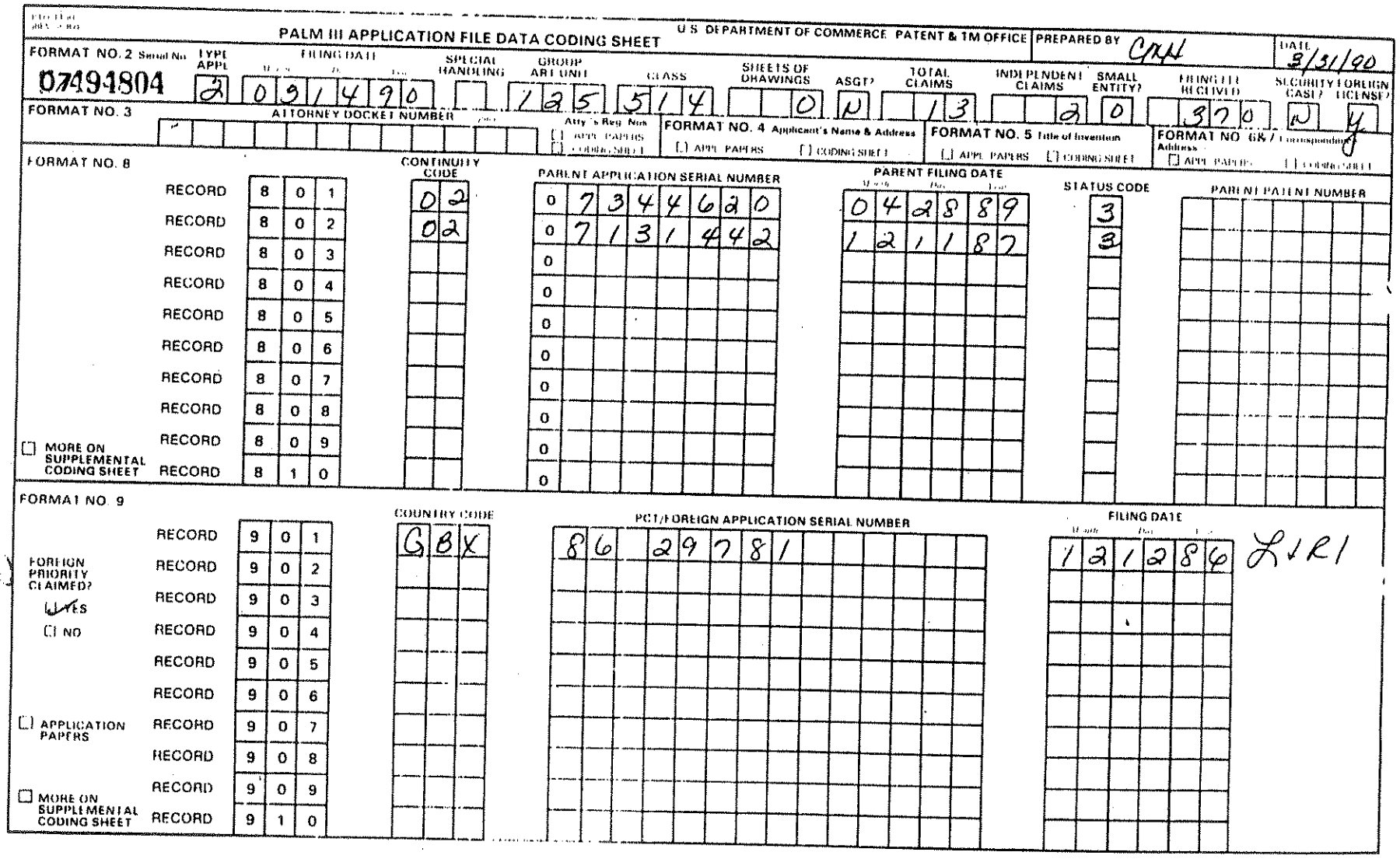
* If the entry in Col. 1 is zero enter zero in Col. 3 (enter "0" in Col. 3)

** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter 20

*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter 3

**** If the entry in Col. 1 is less than the entry in Col. 2, enter zero. If the entry in Col. 1 is greater than the entry in Col. 2, enter the difference.

51



PALM III APPLICATION FILE DATA CODING SHEET

U.S. DEPARTMENT OF COMMERCE PATENT & TM OFFICE

PREPARED BY: CAH

DATE: 3/31/90

FORMAT NO. 2 Serial No.: 07494804

TYPE APPL	FILING DATE	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWINGS	ASGT?	TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FRINGE RECEIVED	SECURITY FOREIGN CASE?	LICENSE?
2	09/14/90		1251	514	0	N	13	2	0	370	N	Y

FORMAT NO. 3 ATTORNEY DOCKET NUMBER: [ ] APPL. PAPERS [ ] CODING SHEET

FORMAT NO. 4 Applicant's Name & Address: [ ] APPL. PAPERS [ ] CODING SHEET

FORMAT NO. 5 Title of Invention: [ ] APPL. PAPERS [ ] CODING SHEET

FORMAT NO. 6 & 7 Correspondence Address: [ ] APPL. PAPERS [ ] CODING SHEET

FORMAT NO. 8

	RECORD	CONTINUITY CODE	PARENT APPLICATION SERIAL NUMBER	PARENT FILING DATE	STATUS CODE	PARENT PATENT NUMBER
	801	02	07347462	04/28/89	3	
	802	02	07131442	12/18/87	3	
	803					
	804					
	805					
	806					
	807					
	808					
	809					
[ ] MORE ON SUPPLEMENTAL CODING SHEET	810					

FORMAT NO. 9

	RECORD	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FILING DATE	
	901	GBX	8629781	12/28/86	L1R1
FOREIGN PRIORITY CLAIMED? [ ] YES [ ] NO	902				
	903				
	904				
	905				
	906				
[ ] APPLICATION PAPERS	907				
	908				
	909				
[ ] MORE ON SUPPLEMENTAL CODING SHEET	910				

G 000168

82

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/[illegible]804	03/14/90	LONG, D	

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

EXAMINER	
FRIEDMAN, S	
ART UNIT	PAPER NUMBER
125	9

DATE MAILED: 05/04/90

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-3+5-4 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims all are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

53

EXAMINER'S ACTION

OL-328 (Rev. 8-89)

Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"Also containing ethanol (claim 1) is indefinite as to what else is included. The claims should state how the pH is arrived at.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited in accord with the entire disclosure. See MPEP 706.03(n) and 706.03(z).

All claims should recite amounts for all ingredients.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

54

All claims are rejected under 35 U.S.C. 103 as being unpatentable over Chem. Absts. all.

The art teaches the cojoined use of use of ranitidine and an alcohol (ethanol). The claims also teach ranitidine and ethanol. The various parameters of the claims; i.e. pH and amounts are considered as choices to one skilled in the art. Such parameters have not been demonstrated as being critical and as such are considered to be within the skill of the art.

All of the claims are rejected over the claims of Serial No. 131,42? on the grounds of double patenting (35 USC 101). No second invention is seen to residue in the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Friedman whose telephone number is (703) 557-9592.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 557-3920.

04/30/90;dal

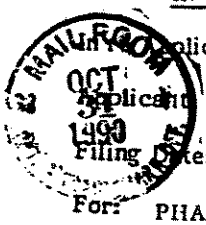
Stanley J. Friedman
Primary Examiner
Group Art Unit 125

59

430.00-117 122-5-4-2/25 Status-041

#10 JRL 11/21/90

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Application Serial No.: 07/494,804

Applicant: David R. LONG

Filing Date: 03/14/90

Group Art Unit: 125

Examiner: FRIEDMAN

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☐ one month ☒ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 430.00.

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200. A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☐ Response ☐ Notice of Appeal ☐ Appeal Brief

☐ _____

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500
REF/er

Date: October 31, 1990

54

120 LA 11/13/90 07494804 1 117 430.00 CK

G000172

11/21 JLP 11/21/90

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LONG

Serial No. 07/494,804

Filed: March 14, 1990

For: PHARMACEUTICAL COMPOSITIONS

Examiner: Friedman, S.

Group Art Unit: 125

AMENDMENT

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This is in response to the Official Action dated May 4, 1990, the period for response to which has been extended to expire on November 4, 1990, by the filing herewith of a Petition for a three month extension of time and and payment of the required fee. Please amend the above-identified application as follows.

IN THE CLAIMS:

Claim 1, line 2, before 'of ranitidine' please insert --an effective amount--;

Line 4, please delete "also containing" and insert --comprising--.

Please cancel claims 8-11 and insert the following claims therefor:

8 ~~15.~~ A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20-400 mg ranitidine per 10 ml dose expressed as free base.

9 ~~16.~~ A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20-200 mg ranitidine per 10 ml dose expressed as free base.

10 ~~17.~~ A pharmaceutical composition as claimed in cliam 1, wherein the effective amount is 150 mg ranitidine per 10 ml dose expressed as free base.

57

REMARKS

Applicant has amended the claims in order to more particularly define the invention, and in consideration of the comments contained in the outstanding Official Action. Claim 1 has been amended to indicate that the ranitidine is present in an effective amount and to delete the objected to terminology "also containing." Claim 8 has been cancelled from the application as being redundant. Claims 10-11 have been cancelled from the application and replaced by claims 15-17 which depend from claim 1. All of the claims now present in the application (claims 1-3, 5-7 and 12-17) are believed to be in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

More particularly, the outstanding Official Action sets forth a rejection of claims 1-3 and 5-10 under 35 U.S.C. 112, second paragraph, for the inclusion of the phrase "also containing alcohol" in claim 1. Applicant has amended claim 1 to replace the objected to terminology with the language "comprising." Accordingly, it is respectfully requested that this aspect of the rejection be withdrawn.

The Official Action indicates that the claims should state how the pH is arrived at. This aspect of the rejection, having been carefully considered, is most respectfully traversed. Applicant respectfully submits that the specification clearly teaches that pH may be adjusted by the use of buffer salts but the specification is equally clear that this is only a preferred way of adjusting the pH. If the solution is prepared using ranitidine free base as input material, then the desired pH may be obtained by the addition of a physiologically acceptable acid such as hydrochloric acid. Alternatively, if the input material is ranitidine hydrochloride, then the desired pH may be obtained by addition of the required amount of a physiologically acceptable base such as sodium hydroxide. These possibilities would be immediately apparent to one of ordinary skill in this art. These possibilities also demonstrate the fact that the precise means by which the desired pH is adjusted is not an essential feature of the invention. Accordingly, it is respectfully requested that this aspect of the rejection be withdrawn.

Claims 1-3 and 5-12 stand rejected for failing to recite amounts of ingredients. Claim 1 has been amended to indicate that the ranitidine is present in an effective amount.

58

In addition, claims 15-17 specifically recite amounts of ranitidine present. Accordingly, it is respectfully requested that this rejection be withdrawn.

All of the claims in the application stand rejected under 35 U.S.C. 103 as being unpatentable over the Chemical Abstracts citation. This reference is said to teach the cojoined use of ranitidine and an alcohol (ethanol). The various parameters of the claims, such as pH and amounts, are considered by the Official Action as choices to one of ordinary skill in the art. The Official Action concludes that such parameters have not been demonstrated as being critical and therefore they are considered to be within the skill of the art. This rejection, having been carefully considered, is most respectfully traversed.

At the outset, Applicant specifically traverses the statement in the Official Action that the references relied upon by the Examiner teach the cojoining of ranitidine and an alcohol, e.g., ethanol. Applicant most respectfully submits that the art does not teach the cojoining of ranitidine and an alcohol and pharmaceutical composition which is an aqueous formulation for oral administration. These references do not lead one of ordinary skill in the art in any way to expect that stability of ranitidine in an aqueous oral formulation could be enhanced by the presence of ethanol and does not suggest the presence of ethanol in such compositions.

The first Chemical Abstract reference (97, 61014G) relates to a new polymorphic form of ranitidine hydrochloride (designated form 2) and includes a description of processes for its production. Applicant most respectfully submits that all that one of ordinary skill in the art would be able to infer from this reference is that ranitidine hydrochloride must be reasonably stable in ethanol since ethanol is used as a solvent for recrystallization. However, there is no teaching whatever that the stability of ranitidine or its salts as an aqueous formulation for oral administration is enhanced by the presence of ethanol and there is no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed.

The second Chemical Abstracts reference (104 102280Z) relates to a paper in a Scandinavian journal indicating that the presence of ethanol in a person's diet did not

59

adversely affect the gastric acid secretion inhibiting properties of ranitidine. Again, there is absolutely no teaching in this reference that would lead one of ordinary skill in the art to expect that ethanol would enhance the stability of ranitidine in aqueous oral formulations or would suggest to one of ordinary skill in the art that ethanol should be added to such formulations.

In summary, the prior art relied upon in the rejection is, in fact, extremely far removed from the presently claimed invention and in no way renders it obvious. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicant wishes to reiterate that the stability of a pharmaceutical formulation for oral administration is the most important factor, and enhancing the stability of the active ingredients of such formulations is always an objective. Thus, in the development of any pharmaceutical formulation, it is necessary to ensure that the drug substance is stable within the formulation, which is necessary for two main reasons. Firstly, the drug substance must be stable in order to ensure that the patient is receiving the correct dosage of the drug. Secondly, it is important to ensure that the patient is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This second point is particularly important since it is not always possible to identify fully all of the breakdown products that may occur. Consequently, the chronic toxicity of all the various compounds arising from the breakdown of the drug substance cannot be determined.

In practice, degradation of the drug substance within a formulation usually occurs upon storage and is often dependent upon a number of factors including temperature and time of storage. Any improvement that can be made in enhancing the stability of the drug substance can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, enhancement of the stability of the drug substance also benefits from the economic point of view in that it increases the effective shelf life of the product. There is not even the most remote suggestion of this in the prior art of record.

60